

6

Docket No. GP-100C1  
Serial No. 08/860,844Remarks

Claims 28, 57 and 62-65 were previously pending in the subject application. By this Amendment, the applicants have amended claims 28 and 62-65. Accordingly, claims 28, 57, and 62-65 remain before the Examiner for his consideration.

Support for these amendments can be found throughout the subject specification and in the previous claims. The amendments to the claims have been made in an effort to lend greater clarity to the claimed subject matter and to expedite prosecution. These amendments should not be taken to indicate the applicants' agreement with, or acquiescence to, the rejections of record. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

The claims currently pending in the subject application are drawn to the applicants' unique system for specifically binding double stranded portions of a target nucleic acid molecules. The Target Binding Assemblies (TBAs) of the subject invention are made up of multiple nucleic acid recognition units each of which binds without great affinity to discrete target sequences. The multiple nucleic acid recognition sites are directed to discrete sequences on the double stranded portion of a target nucleic acid molecule. When the multiple nucleic acid recognition sites bind, each with relatively low affinity, to their corresponding target sequences, the combined effect is that the entire TBA (with its multiple nucleic acid recognition units) binds with great affinity and specificity to the double stranded portion of a target nucleic acid molecule.

Thus, the effectiveness of the TBAs of the subject invention can be attributed to the TBAs having multiple binding components that act cooperatively. Although the individual TBA components bind relatively weakly, the entire TBA binds with great strength as the individual TBA binding components are cooperatively bound together.

The system of the subject invention is particularly unique and advantageous because the TBA binds selectively to a double stranded portion of a target nucleic acid molecule, and discriminates for this target compared to a different (non-target) region, even if the different (non-target) region contains sequences within it which are identical to sequences in the target binding region.

The structural features of the TBA make it possible to, for example, target an individual control region and not interfere with other cellular sites that contain (even exactly identical)

NDN/la

individual binding sites that are present in the targeted control region. Specifically exemplified in the subject application is a TBA directed to the HIV-LTR. The exemplified TBA contains a down-shifted binding unit of NF-kB (or binding portion of such) and down-shifted binding units of SP1. Despite the existence of other sites in the human genome having an NF-kB binding site (e.g., the beta2-micro-globulin promoter, the kappa-light chain promoter, etc.), the TBA for HIV advantageously does not compete for the NF-kB binding sites in the human genome because these other binding sites do not have all of the sequences targeted by the multiple nucleic acid recognition sites of the HIV-LTR TBA.

In view of the unique structural and functional characteristics of the applicants' technology, as reflected by the current claims, the applicants respectfully request favorable consideration of the claims now pending.

Claims 63 and 65 have been rejected under 35 U.S.C. §112, first paragraph. The Office Action indicates that the use of the words "all of" constitutes "new matter" and/or is not in compliance with the "written description" requirement of 35 U.S.C. §112, first paragraph. The applicants respectfully submit that the specification (including the figures), as filed, contains support for the "all of" limitation.

Please note that there is no requirement that the claim technology must be present verbatim as used in the specification. It is well settled in the patent law that the claim language of an amendment need not be disclosed word for word in a specification. *In re Wilder*, 222 USPQ 369, 372 (Fed. Cir. 1984) ("It is not necessary that the claimed subject matter be described identically, but the disclosure must convey to those skilled in the art that applicant had invented the subject matter later claimed.") (emphasis added); see also MPEP §2163.02.

It is also well-settled that the written description requirement of 35 U.S.C. §112, first paragraph, can be satisfied without express or verbatim disclosure. See, e.g., *In re Herschler*, 591 F.2d 693, 700, 200 U.S.P.Q. 711, 717 (CCPA 1979): "The claimed subject matter need not be described *in haec verba* to satisfy the description requirement. It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations." (citations omitted). See also *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320,

VDNJA

1323, 56 U.S.P.Q.2d 1481, 1483 (Fed. Cir. 2000) ("In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue.").

Nevertheless, in order to expedite prosecution, and because the recitation of "all of" does not appear to lend greater clarity to the claimed invention, this term has been removed from the claims. Accordingly, the applicants respectfully submit that this rejection has been rendered moot.

Claims 28, 57 and 62-65 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The applicants respectfully request reconsideration of this rejection to the extent that it might be applied to the current claims. Please note that the claims have been amended herein to clarify that the TBAs of the subject invention specifically bind to target sequences but not to non-target sequences. This ability to discriminate between target and non-target sequences is critical to the current invention and is emphasized throughout the specification.

In addressing the degree of clarity required of patent claims, the Federal Circuit has stated:

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, §112 demands no more. The degree of precision necessary for adequate claims is a function of the nature of the subject matter. *Miles Lab., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993) (internal citations omitted).

The applicants respectfully submit that the claims as currently presented are certainly sufficiently precise to apprise those skilled in the art of the metes and bounds of the claimed subject matter. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112 second paragraph.

Claims 63-65 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Lamarco *et al.* (U.S. Patent No. 5,453,362); taken in view of Jamieson *et al.* 1994 (*Biochemistry* 33:5689) and Desjariasis *et al.* 1993 (*Proc. Natl. Acad. Sci. (USA)* 90:2256) and further in view of Krizek *et al.* 1991 (*J. Am. Chem. Soc.* 113:4518). The applicants respectfully traverse this ground for rejection because the cited references, alone or in combination, do not disclose or suggest the claimed invention.

As set forth in the applicants' claims, the specificity of the TBAs of the subject invention

VJNB/a

results from assembling multiple, low binding affinity domains into a single molecule. Because the binding of the target by a TBA is accomplished by the cooperative binding of weak binding domains that bind side-by-side on targets to create a high-affinity, target-specific binding assembly, TBAs bind tightly to the target only when the entire target is present and all binding components of the TBA are bound. The cited references do not disclose or even suggest such a unique and advantageous system.

A single binding protein binds wherever its binding site is present and does not provide a basis for discriminating, for example, a viral genome from the host cell background genome. The claimed method is based on TBAs that specifically bind to a target made up of individual binding components that are assembled into a specific spatial pattern (such as a viral promoter or cellular enhancer), even when the individual binding components may be separately found in many places in the background genome.

Example 9 (Production of "High-Order" TBAs) of the applicants' specification, a portion of which is reproduced below, provides an excellent example of the subject invention and how a TBA can discriminate a target which includes, as a portion, a binding site that is identical to a site found in the background genome.

Because of this extremely high affinity for the HIV-LTR that can be generated using a multimeric TBA, the compounds having this structure and which can be used for this purpose are referred herein as "HIV-Lock."

An optimal HIV-Lock is defined by footprinting (according to methods well known in the art) TBAs bound to TBRs in the HIV LTR to confirm that the binding affinity of each DNA binding protein contributing to the formation of the multimeric TBA complex is downshifted relative to the affinity for any natural target sequence (i.e., CNAs) from which the DNA binding recognition unit of the TBA is derived. Any concomitant loss in binding affinity for the HIV TBRs is more than compensated for upon formation of the multimer as described below.

There may be competition between the binding of each component TBA for its TBR and assembly, via asymmetry sequences to form the multimer. This is obviated by adjusting the linkers between the chaperone and asymmetry sequences in each TBA component such that these competing events are uncoupled. The resultant reduction in the dimensionality of diffusion (effective concentration increase) for the TBA asymmetry and assembly components results in efficient formation of the multimeric complex.

MDN3/3

On the basis of footprinting, the length and composition of linkers is adjusted to achieve optimal discrimination between target HIV sequences and natural sequences. In this fashion, although each component TBA will have a low affinity for CNA and TBR sequences, the multimeric complex will have an extremely high affinity for the now expanded TBR recognized by the multimeric complex (the square of the affinity of each TBR recognized by each component TBA of the multimeric TBA) while still having a low affinity for CNAs. In the same fashion, other multimeric TBA complexes, aside from HIV-Lock, are prepared.

In the HIV-Lock example, a TBA discriminates targets from similar but different cousin targets. These cousin targets may contain identical binding sites that are also found in the TBR. For example, in accordance with the subject invention as claimed, it is possible to discriminate the HIV-LTR (with its two adjacent NF-kB binding sites next to three adjacent SP1 binding sites) from other sites containing identical NF-kB binding sites (such as in the Beta-2-microglobulin promoter as well as in the Kappa-light chain promoter in the human genome). This method for constructing TBAs is not only unobvious, it is counterintuitive – it requires downshifting the affinity of the TBA components to generate a high binding affinity and selectivity of the assembled TBA for the entire target. This allows HIV-Lock to target the HIV control region (HIV-LTR) without interfering with normal cellular transcription factor trafficking through cousin sites such as the beta-2 microglobulin and kappa-light chain promoters.

A TBA is effective because it is composed of multiple binding components that are cooperatively bound together. Although the individual TBA components bind weakly, the entire TBA binds with great strength and specificity as the individual TBA binding components are cooperatively bound together. This feature of a TBA allows it to target an individual control region and to not interfere with other cellular sites that contain (even exactly identical) individual binding sites that are present in the targeted control region.

Lamarco *et al.* identify and describe a single nucleic acid binding protein, Host Cell Factor (HCF). In the summary of the invention (column 2, lines 21-36), Lamarco *et al.* state that HCF is required for transcription of a number of genes containing the TAATGARAT binding site. The sole basis for binding site recognition specified by Lamarco *et al.* is the recognition of the TAATGARAT binding site by the full length HCF protein or one of its truncated forms (column 4, lines 20-26,

WNI/va

column 8, lines 51-67). The reference to fusion proteins (column 6, lines 46-65) simply refers to fusions specifically related to the expression, processing and transport in eukaryotic cells and does not relate to either the recognition or the specificity of recognition of the HCF protein for TAATGARAT alone or in its genomic context. For example, as can be seen from human chromosome 13 from the NCBI database (<http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=13989969>), there are multiple TAAGARAT sites in chromosome 13 (e.g. positions 34,239-34,247, 43923-43931, 47283-47291, 55895-55993, 73532-73540, 89068-89076 and 111012-111020). It is clear that any molecule based on HSF or a portion of HSF would interact with both viral and cellular targets and would not be capable of discriminating between the two. Because Lamarco et al. does not teach how to bind to a defining feature of the virus not present in the background genome, molecules based on HCF recognition of the TAATGARAT site alone can be expected to have no utility *in vivo* as a therapy.

The same argument holds for Jamieson et al. [Biochemistry 33:5689 (1994), Desjarlais et al. [Proc. Natl. Acad. Sci. (USA) 90:2256 (1993)] and Krizek et al. [J. Am. Soc. 113:4518 (1991)]. The zinc finger DNA binding proteins (e.g. sp1), either naturally occurring or redesigned as in the referenced articles above, bind to sites that occur also in the reference genome. The "three finger motif domains" of Desjarlais et al. can not and do not correspond to the cooperatively bound binding units of the TBAs as the individual zinc fingers alone have no specificity (as the examiner points out) and together they act as a single binding domain for their target sequence. Zinc finger binding sites are present multiple times in most genomes and are always present in both viral and cellular genomes. This is due to the fact that viruses that integrate into the host cell genome utilize host cell transcription factors for activation.

Again, the case of HIV-LOCK can be used to sort and illuminate the issues. In the HIV-LTR, there are two NFkB binding sites and three sp1 binding sites. Sp1 is a three zinc finger, DNA-binding protein. Sp1 binds independently to each GC box sequence and physical interaction between adjacent sp1 molecules is insufficient to give rise to cooperative DNA binding behavior (Narayan, et al. [Journal Biol. Chem. 272:7801 (1997)], page 7801, column 2, lines 6-9). Sp1 alone cannot be used to recognize the HIV LTR as there are multiple sp1 binding sites not only in the HIV LTR but also in the human genome. A therapy based on sp1 alone must fail as any attempt to modulate the

UNN/la

activity of a spl binding site in the HIV LTR using spl would also interfere with the regulation of genes whose promoters contain spl. This is true for any protein comprised of three zinc fingers.

Any effective therapy has to address the issue of non-interference with normal cellular trafficking of transcription factors. Effective and useful therapies cannot be made simply by using proteins that could be expected to affect cellular regulation. Neither Lamarco, Jamieson, Desjarlais nor Krizek disclose or suggest a method to selectively bind and therefore modulate the activity of a viral target nucleic acid without affecting the host cell genome.

It has been well established in the patent law that the mere fact that the purported prior art could have been modified or applied in some manner to yield applicant's invention does not make the modification or application obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). However, as expressed by the CAFC, to support a §103 rejection, "[b]oth the suggestion and the expectation of success must be founded in the prior art ..." *In re Dow Chemical Co.* 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988). As is clearly shown by the foregoing remarks, one finds neither the suggestion nor the expectation of success in Stratford *et al.* or Allen *et al.*, either separately or combined. An assertion of obviousness without the required suggestion or expectation of success in the prior art is tantamount to using applicant's disclosure to reconstruct the prior art to arrive at the subject invention. Ilindsight reconstruction of the prior art cannot support a §103 rejection, as was specifically recognized by the CCPA in *In re Spinnoble*, 56CCPA 823, 160 USPQ 237, 243 (1969).

Advantageously, the TBAs of the current invention provide a mechanism for distinguishing between sites contained within a target sequence and its background because the TBA can assemble elements that not only recognized the target site but also its context (i.e. flanking sequences) allowing for the specific binding of a target to the exclusion of the background genome in a manner similar to HIV-Lock. HIV-Lock, is made with multiple binding components for adjacent sites within the HIV LTR. TBAs, such as HIV-Lock, can be used to bind to the target site and to exclude sites which have an identical portion of, but not all of, the target site. The subject invention provides a unique and advantageous means to modulate the activity of a nucleic acid sequence without interfering with normal cellular transcriptional activity.

VDNIM/a

13

Docket No. GP-100C1  
Serial No. 08/860,844

Claim 65 has been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/407,543. Please note that the applicants are submitting herewith a Terminal Disclaimer with regard to copending Application No. 10/407,543, filed April 3, 2003.

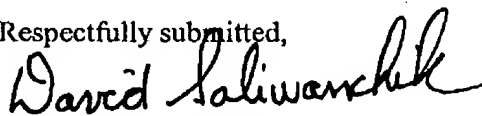
The submission of this Terminal Disclaimer is being done to expedite prosecution and should not be taken to indicate the applicants' agreement with, or acquiescence in, the double patenting rejection. In view of the submission of this Terminal Disclaimer the applicants respectfully submit that the obviousness-type double patenting rejection has been rendered moot.

In view of the foregoing remarks and the amendments above, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicant also invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



David R. Saliwanchik

Patent Attorney

Registration No. 47,545

Phone: 352-375-8100

Fax No.: 352-372-5800

Address: P.O. Box 142950

Gainesville, FL 32614-2950

DRS/la

Attachment: Terminal Disclaimer

UNIV/la